INTERVIEW SUMMARY

The Applicants would like to thank the Examiner for the telephone interview on June 2, 2005 with Dr. Alan Wahl and Applicants' representative, Vita Conforti. During the interview, Dr. Wahl and Ms. Conforti distinguished the claims from Pohl *et al.* The Examiner and the Applicants agreed that Pohl *et al* is the primary reference to overcome. Also, the Examiner and the Applicants agreed that Pohl *et al* did not teach or suggest "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent and in the absence of cells other than cells of said Hodgkin's Disease cell line."

REMARKS

Claims 1-8, 11, 13-19 and 67 are pending in the present application.

The Applicants would like to thank the Examiner for withdrawing the rejection under 35 USC 112, first and second paragraph, of claim 67; the rejection of the claims under 35 USC 102(b) as being anticipated by WO 96/22384; the rejection of claims 1-5, 7, 8, 11, 13, 15, 16, and 19 under 35 USC 103(a) as being unpatentable over WO 96/22384 and further in view of Barth *et al*; and the double patenting rejection.

Section headings have been added in this Amendment for organizational purposes.

Specification

The Examiner has objected to the disclosure because it, for example, at page 30 line 26 contains an embedded hyperlink and/or other form of browser executable code. The Applicants have carefully reviewed the entire specification and deleted any embedded hyperlink and/or other form of browser executable code.

Claim Rejections – 35 USC 112

The Examiner rejected claims 8 and 13-19 under 35 U.S.C. 112, first paragraph, for allegedly "not reasonably provide enablement for any other anti-CD[30] antibodies for the method of treating Hodgkin's disease." The Examiner indicates that this rejection can be overcome by a deposit of the cell lines along with an affidavit or declaration stating that the deposit has been made under the terms of the Budapest Treaty and that all

restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Without acquiescing to the rejection, and merely to expedite prosecution, the Applicants have amended the specification to show that a deposit of the hybridoma has been made and to include the identifying information set forth in 37 CFR 1.809(d). Additionally, the Applicants provide herewith a Statement that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Further, pursuant to 37 CFR 1.802(b) (MPEP 2404.01), Hefi-1 is both known and readily available to the public. Hefi-1 is publicly available from the Biological Resources Branch, DCTD NCI-Frederick Cancer Research and Development Center, P.O. Box B, Building 1052, Room 253, Frederick, MD 21702-1201, FAX: 301-846-5429.

A verified statement by Dr. Philip Tsai is enclosed corroborating that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification, and was in the Applicants' possession at the time the application was filed.

In addition to the deposit having been made, the Applicants do not acquiesce that the application as filed does not contain sufficient enablement for how to make anti-CD30 antibodies for the method of treating Hodgkin's disease. Rather, the application is replete with examples and disclosure on how to make the antibodies of the claimed invention at least from page 13, lines 17 thru page 21, line 11. For example, the application describes at least the production of monoclonal antibodies using a wide variety of techniques including the use of hybridoma, recombinant, and phage display technologies; methods for producing and screening for specific antibodies using hybridoma technology; methods for producing and generating antibody fragments; methods for generating chimeric, humanized, and human antibodies; and methods to generate anti-idiotype antibodies. Further, the application describes binding assays at least on page 21, line 14 through page 23, line 23; assays for cytotoxic and cytostatic activities on page 23, line 24 through page 25, line 20; and methods of producing the

proteins of the invention on page 31, line 14 through page 36, line 14. Therefore, Applicants respectfully assert that the application as filed contains sufficient enablement for how to make anti-CD30 antibodies for the method of treating Hodgkin's disease.

The specification of the application enables the instant claims. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

In the application of the law of enablement to antibody-related inventions, the Examiner's attention is directed to *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), in which the Federal Circuit reversed a Patent Office rejection of claims directed to immunoassays of hepatitis B surface antigen using high affinity monoclonal IgM antibodies for lack of enablement. The court concluded that, even without a hybridoma deposit, undue experimentation would not be required to practice the invention. In arriving at its decision, the court noted that the finding of enablement was "consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980." *Wands*, 858 F.2d at 736, citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94.

Claim Rejections – 35 USC 103

The Examiner rejected claims 1, 2, 5, 7-13, 16, 19 and 67 under 35 USC 103(a) as being unpatentable under Pohl *et al* (1993, *CD30-specific AB1-AB2-AB3 Internal Image Antibody Network:Potential Use as Anti-Idiotype Vaccine Against Hodgkin's Lymphoma,* Int. J. Cancer, vol. 54, pages 418-425). Applicants respectfully traverse the rejection.

The Examiner recites that Pohl *et al* allegedly teach

> "(1) Hodgkin's disease treatment art ...suggest an active immunotherapy to solve the high rate of relapse using an antibody binding to CD30 by administering an anti-CD30 antibody binding CD30 expressed in of Hodgkin's disease (note 1st paragraph); (2) "murine monoclonal ab2ß 9210, 14G9 induced a CD30 specific T- and B-cell response" in vivo at page 418, left column, 1st paragraph; (3) AB3 4A4 antibody at Figs. 7-10 that exerts cytotoxic effect on Hodgkin's disease cell lines in the absence of conjugation to cytotoxic agent, and prevent tumor-cell growth in vivo model.
> Therefore, it would have been obvious to use ab2ß 9G10, 14G9, AB3 4A4 for treating patient with Hodgkin's disease...suggesting phase-1 clinical trial for Hodgkin lymphoma at the last line at page 425."

Applicants' respectfully assert that Pohl *et al* cannot render the present claims obvious at least because Pohl *et al* fail to suggest (1)(a) an antibody immunospecific for CD30; (1)(b) a protein which competes for binding to CD30 with monoclonal antibody AC10 or HeFi-1; (2) which exerts a cytostatic or cytotoxic effect in the absence of cells other than cells of said Hodgkin's Disease cell line; and (3) a method for the treatment of Hodgkin's disease.

Pohl *et al* describe a vaccine, active immunity approach

Pohl *et al* described the use of the anti-idiotype antibody as a vaccine. The binding site on some anti-idiotype antibodies, Ab2, resembles the structure of the epitope on the original antigen. Such anti-paratope antibody can interact with B cells specific for the original antigen, thus inducing production of more antibody against the antigen.

Active immunization is believed to elicit protective immunity and immunological memory so that a subsequent exposure to the pathogenic agent will elicit a heightened immune response with successful elimination of the pathogen. Active immunization can be acquired artificially through administration of a vaccine. In active immunization, the immune system plays an active role, with proliferation of antigen reactive T and B cells resulting in formation of memory cells.

On the other hand, passive immunization involves the transferring to a recipient of preformed antibodies.

Pohl *et al* discusses the use of anti-idiotype antibodies

The use of anti-idiotypes by Pohl *et al* is an extension of the "network theory" of Niels Jerne proposed in 1973 for which Jerne received the Nobel Prize in 1984. According to the network theory, as antibody is produced in response to an antigen, it in turn induces the formation of antibodies to its unique variable region sequences. Jerne referred to each individual antigenic determinant of the variable region as an idiotope. Each antibody contains multiple idiotopes, and the sum of the individual idiotopes is called the idiotype of the antibody. In some cases, a particular idiotype and the actual antigen combining site, which Jerne called the paratope, are identical.

Ab1 (primary antibody), Ab2 (anti-idiotype antibody), and Ab3 (anti-anti-idiotype antibody)

The network theory proposes that during a humoral response the antibodies formed in response to the antigen in turn induce the formation of secondary antibodies to the individual idiotopes of the first (primary) antibody. The idiotype of the primary antibody, Ab1, activates a network of B cells whose receptors recognize the individual idiotypes of Ab1. These B cells then differentiate into plasma cells that secrete anti-idiotype antibody (Ab2). The individual idiotype of Ab2 can then further extend the network by inducing production of an anti-anti-idiotype, or Ab3.

A central principle of the network theory is that some anti-idiotype antibody will be directed against the paratope and therefore will appear as the internal image of the original epitope on the antigen. Pohl *et al* describe the use of anti-idiotype antibodies as vaccines. Immunization with anti-idiotype antibody theoretically provides a way for exposing an individual to an epitope, without risking exposure to a pathogen.

The following is a cartoon taken from Schoenfeld, *Nature Medicine,* 10:1 (2004), pg 17 showing the relationship among an Ab1, Ab2, and Ab3:

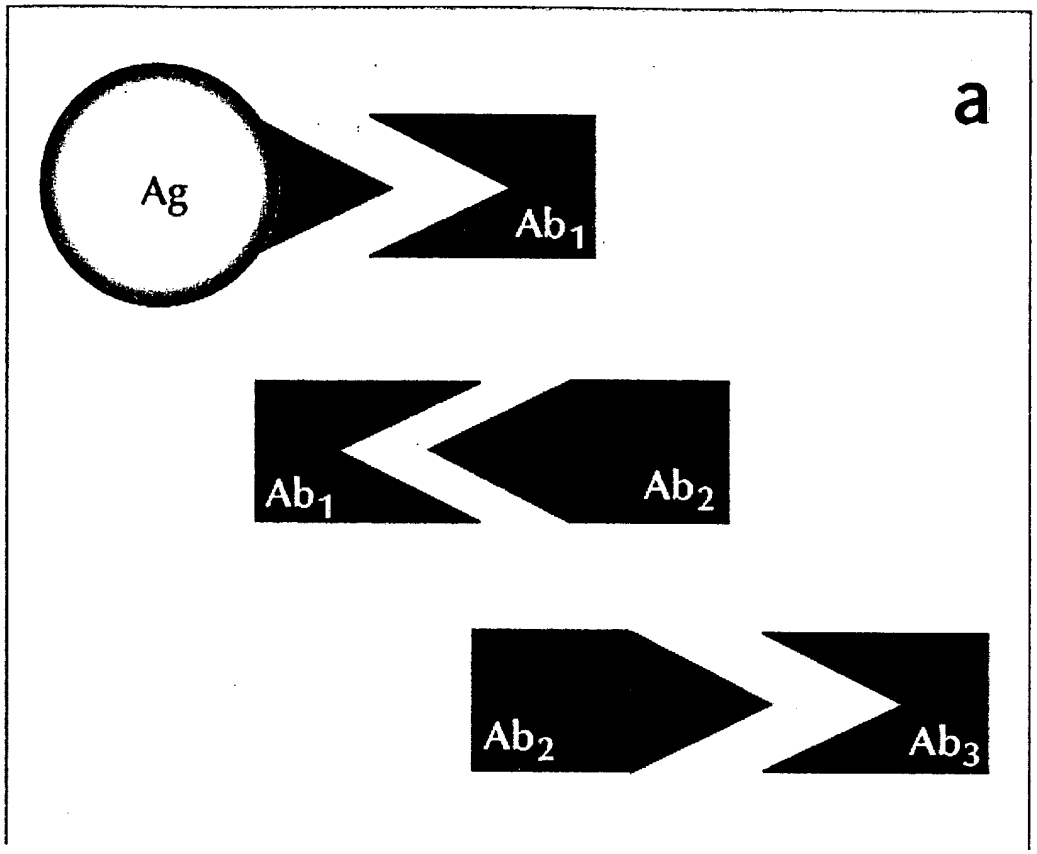


Figure 1. Chain of antibodies.

(**a**) According to Jerne's theory of the idiotypic network, immunization with an antigen may lead to the generation not only of antigen-specific antibodies (Ab_1), but also to antibodies that recognize Ab_1. This occurs because the unique structure (idiotype) of the antigen-binding site of Ab_1 stimulates the immune system to generate Ab_2, which mimics the structure of the antigen. Eventually, a similar mechanism generates Ab_3. Ab_1 and Ab_3 have similar binding capacities and, in many cases, identical amino acid sequences at their antigen-binding sites.

The following table shows the Ab1, Ab2, and Ab3 antibodies as discussed by Pohl *et al*:

Network theory designation	Antibody name	Specificity	Property
Ab1	HRS-4	Anti-CD30	Does not "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line" in the absence of "cells other than cells of said Hodgkin's Disease cell line"; requires NK cells (see Pohl *et al*, pg. 422, right column, lines 34-38 and Affidavit of Alan Wahl, para. 9 and 9a)
Ab2	9210 14G9	Mirrors the CD30 antigen; immunospecific for HRS-4 (see Pohl *et al*, page 418, left column, first paragraph, lines 25-29 and page 420, right column, lines 23-25)	Does not "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line" in the absence of "cells other than cells of said Hodgkin's Disease cell line"; requires the presence of B cells and T cells (see Pohl *et al*, page 418, left column, 1st paragraph and Affidavit of Alan Wahl, para. 11 and 11a).
Ab3	4A4	Anti-CD30	Does not "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line" in the absence of "cells other than cells of said Hodgkin's Disease cell line"; requires the presence of complement and/or effector cells (see Pohl *et al*, at least, pg 424, Figures 8 and 9 and Affidavit of Alan Wahl, para. 10 and 10a)

Pohl *et al* do not suggest administration of an anti-CD30 antibody

The Examiner recites that Pohl *et al* allegedly teach "an active immunotherapy to solve the high rate of relapse using an antibody binding to CD30 by administering an anti-CD30 antibody binding CD30 expressed in of Hodgkin's disease (note 1st paragraph)." The Applicants respectfully assert that Pohl *et al* do not suggest administration of an anti-CD30 antibody, but active immunotherapy using an anti-iditotypic antibody. An anti-idiotypic antibody is not an anti-CD30 antibody, but one which mirrors the confirmation of the original antigen. (See, Pohl *et al,* Abstract, lines 1-3, "The tumor-associated CD30 antigen is presently under study as a target for active specific immunotherapy of Hodgkin's lymphoma with anti-idiotypic antibodies" and page 418, left column, first paragraph, lines 25-29). The Ab2ß antibodies are not immunospecific for CD30. Rather, they are specific for the Ab1 HRS-4. Pohl *et al,* page 420, right column, lines 23-25; *see also* Figure 3, page 421, "Inhibition of monoclonal Ab1 binding to Ab2 by Ab3". Therefore, the Applicants respectfully assert that Pohl *et al* cannot render claims 1, 8, 11, or 67 obvious (claim 1 "...an antibody that (i) immunospecifically binds CD30..."; claim 8 "competes for binding to CD30 with monoclonal antibody AC10 or HeFi-1"; claim 11 "immunospecifically binds CD30"; and claim 67 "(a) an antibody that (i) immunospecifically binds CD30").

Pohl *et al* does not suggest an antibody that exerts a cytotoxic effect on a Hodgkin's disease cell line "in the absence of cells other than cells of said Hodgkin's Disease cell line."

Further, the Examiner recites that Pohl *et al* allegedly teach "murine monoclonal ab2b 9210, 14G9 induced a CD30 specific T- and B-cell response" in vivo at page 418, left column, 1st paragraph. The B cell response of the Ab2 antibodies was the induction of polyclonal antibodies. Whereas, the T cell response was a delayed type hypersensitivity reaction. Each of these responses took place in the presence of B cells and T cells. Affidavit of Alan Wahl, para. 11 and 11a. They did not take place, as claimed in claims 1, 8, 11, and 67, "in the absence of cells other than cells of said Hodgkin's Disease cell line." Therefore, Pohl *et al* cannot render claims 1, 8, 11, and 67 obvious.

The Examiner recites that Pohl *et al* allegedly teach an "Ab3 4A4 antibody at Figs. 7-10 that exerts cytotoxic effect on Hodgkin's disease cell lines in the absence of conjugation to cytotoxic agent, and prevent tumor-cell growth in vivo model." However, the Applicants respectfully assert that the Ab3 antibody requires the presence of complement and/or effector cells (see at least, pg 424, Figures 8 and 9 and Affidavit of Alan Wahl, para. 10 and 10a). Figure 8 on page 424 of Pohl *et al* shows the "complement dependent cytotoxicity induced by Ab3." The Ab3 was incubated with *complement* and the percent lysis was measured. In Figure 8, page 424 of Pohl *et al,* " [a]ntibody dependent cell-mediated cytotoxicity by AB3" was measured. The Ab3 was incubated in presence of peripheral blood lymphoctes as *effector cells* and the percent cell lysis was measured. Therefore, Pohl *et al* cannot render claims 1, 8, 11, and 67 obvious which recite "...in the absence of cells other than cells of said Hodgkin's Disease cell line...".

Pohl *et al* does not suggest a method for "the *treatment* of Hodgkin's Disease..."

Further, as cited by the Examiner, the Ab3 antibody, at best, was able to exert a *preventative* effect and was not shown to treat an established solid tumor. (See, Pohl *et al*, "*Prevention* of tumor growth in vivo by Ab3 4A4", pg 422, right column, line 7; "with regards to the *prevention* of tumor relapse" pg 423, left column, line 25; "in vivo tumor neutralization studies reported here represent a successful *prevention* of solid Hodgkin cell tumors by internal-image" antibody-induced monoclonal Ab3 in vivo" pg 424, right column, lines 2-4.) On page 422, right side column titled *Prevention of Tumor Growth in vivo by Ab3 4A4*, Pohl *et al* tested the ability of Ab3 4A4 to prevent tumor growth *in vivo*. Pohl *et al* describe the pretreatment of SCID mice with 4A4 or HRS-4. (Pohl *et al.*, page 422, right hand column, first full paragraph). One hour subsequent to pretreatment with 4A4 or HRS-4, the SCID mice were subcutaneously injected with a number of L540 tumor cells. The SCID mice still had functioning natural killer cell activity. Pohl *et al*, pg 422, right column, lines 12-14. Pohl *et al* conclude that the 4A4 may "*prevent* the growth of solid CD30+ (L540)-cell tumors" due to complement. Pohl *et al*, pg 422, right column, lines 44-47. Whereas, the HRS-4 may be efficient in the "prevention of tumor growth" due to an NK-cell-mediated mechanism. Pohl *et al*, page 422, right column,

lines 47-50 and Affidavit of Alan Wahl, para. 9 and 9a. In the absence of NK cells, HRS-4 permitted tumor growth. Pohl *et al,* page 422, right column, lines 34-38. Pohl *et al* do not describe a study where SCID mice with established tumors were treated with 4A4 or HRS-4. Pohl *et al* does not suggest treatment of established tumor as in Examples 8 and 9 of the present application. Examples 8 and 9 of the present application show treatment of an established tumor allowed to grow to size of 150 mm^3 and/or were palpable in SCID mice prior to treatment. Therefore, Pohl *et al* cannot render claims 1, 8, 11, and 67 obvious which recite "[a] method for the *treatment* of Hodgkin's Disease...". (emphasis added).

Pohl *et al* does not suggest passive immunization

The Examiner recites that Pohl *et al* allegedly teach that "...it would have been obvious to use ab2b 9G10, 14G9, AB3 4A4 for treating patient with Hodgkin's disease...suggesting phase-1 clinical trial for Hodgkin lymphoma at the last line at page 425." The Applicants respectfully believe that the paragraph on the right hand column of page 425, and particularly the last line, is referring to the use of the Ab2 anti-idiotype antibodies in an active immunotherapy, vaccine approach in any possibly suggested phase-1 study in patients. The title of the article itself postulates the use of an anti-idiotype vaccine against Hodgkin's lymphoma - "*CD30-specific AB1-AB2-AB3 Internal Image Antibody Network: Potential Use as Anti-Idiotype Vaccine Against Hodgkin's Lymphoma*".

Because Pohl *et al* describe an active immunization approach, it fails to suggest an antibody that "exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line" in the absence of "cells other than cells of said Hodgkin's Disease cell line" as recited in claims 1, 8, 11, and 67. Pohl's *et al* entire approach of an active immunization, vaccine approach does not suggest the present claims. Therefore, Applicants respectfully assert that the present claims are unobvious in view of Pohl *et al.*

35 USC 103(a)- Pohl *et al* and further in view of Barth *et al*

The Examiner rejected claims 1, 3, 8, 11, 14, 16, and 18 under 35 USC 103(a) as being unpatentable under Pohl *et al* and further in view of Barth *et al*, (June 2000, Blood, vol. 95, page 3909-14). Applicants respectfully traverse the rejection.

The Examiner recites that Pohl *et al* "do not specifically say "chemotherapy"." Further, the Examiner alleges that Barth *et al* "teach that conventional chemotherapy works quite well in treating Hodgkin's disease..." Barth *et al* describes the use of an immunotoxin of Ki-4 fused to *Pseudomonas* extotoxin A (a cytostatic or cytotoxic agent). Barth *et al* does not suggest an that "exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent." Further, Barth *et al* cannot satisfy the deficiencies of Pohl *et al* described above. Therefore, Applicants respectfully assert that Pohl *et al* and further in view of Barth *et a.*, cannot render claims 1, 3, 8, 11, 14, 16, and 18 obvious.

35 USC 103(a) - Pohl *et al*, in view of Barth *et al*, and further in view of da Costa *et al*

The Examiner rejected claims 1, 4, 6, 8, 11, 15, and 17 under 35 USC 103(a) as being unpatentable under Pohl *et al*, in view of Barth *et al.*, and further in view of da Costa *et al,* 2000, Cancer Chemother Pharmacot, 46(suppl):S33-S36. Applicants respectfully traverse the rejection.

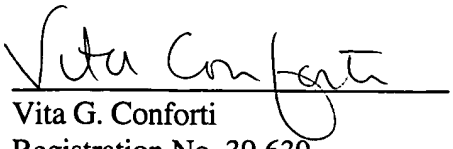
The Examiner recites that neither Pohl *et al* nor Barth *et al* "teach an anti-CD30 antibody of the respective base claims conjugated to cytotoxic agent. However, da Costa et al., teach an anti-CD30 antibody conjugated to an cytotoxic agent...." The Applicants respectfully assert that da Costa does not discuss anti-CD30 conjugates at all. Therefore, Applicants respectfully assert that Pohl *et al*, in view of Barth *et al.* and further in view of da Costa *et al*, cannot render claims 1, 4, 6, 8, 11, 15, and 17 obvious.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicants request that the Examiner call the undersigned attorney at (425) 527-4122 if any questions or issues remain.

Respectfully submitted,



Vita G. Conforti
Registration No. 39,639
Attorney for Applicants

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SEATTLE GENETICS, INC.
21823 30th Drive SE
Bothell, Washington 98021
Telephone: (425) 527-4122
Fax: (425) 527-4123